UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,373	06/21/2002	Isao Ishida	051023-0115	3667

22428 7590 08/31/2004

FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
SHUKLA, RAM R	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 08/31/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,373	ISHIDA ET AL.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *6 and 10-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 September 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of the invention of group I, claims 1-5 and 7-9, drawn to a non-human mammal comprising an exogenous human cytochrome P450 gene in the reply filed on 6/4/04 is acknowledged. The traversal is on the ground(s) that the special technical feature of both group I and II is a non-human mammal comprising a cytochrome p450 gene. This is not found persuasive because as noted in the previous office action, the art already taught a transgenic mouse that comprised human p450 gene and invention of group I does not make a contribution over the prior art. Application's arguments that there will be no undue burden are not persuasive since there will be a search burden for searching a knockout mouse and a mouse expressing exogenous gene. Furthermore, it's not just search burden, it's also an examination burden.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 6 and 10-24 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invetion, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 6/4/04.

3. Claims 1-5 and 7-9 are pending.

4. Claims 2-5 and 7-9 are objected to for not using proper article. For example, claim 2 depends from claim 1, but it recites "A nonhuman mammalian" instead of "The nonhuman mammalian". Appropriate correction in all the claims is required for any term used second time in these claims.

Claims 1-5 and 7-9 are objected to because of improper English use. The term "A nonhuman mammalian" is inappropriate because "mammalian" is an adjective and therefore it should be followed by a noun. Use of a term, such as "A nonhuman mammalian host" is suggested.

Information Disclosure Statement

5. The information disclosure statement filed 6/21/02 fails to comply with 37 CFR 1.98(a)(1), which requires a list of all patents, publications, or other information submitted for consideration by the Office. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-5, 7 and 9 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is drawn to a non-human mammal which harbors at least one human cytochrome p450 gene wherein the expression of the gene is induced by a compound serving as a substrate for a product of the gene. Claim 2 limits the p45o to CYPT3A family while claim 3 and 5 limit how the gene is introduced animal in which the gene encoding GPCR mACHR-6 is misexpressed or how the mammal is produced. Claim 9 recites a cell or tissue of the mammal.

The specification teaches working example of producing a mouse ES cell comprising a fragment of human chromosome 7 that contains the human CYP3A gene and preparation of a transgenic mouse by using the ES cells comprising the human chromosome 7 fragment and characterization of the mice (see examples 2-6). The art does not teach how to make any other mammal and does not teach what are the characteristics of any nonhuman mammal other than a mouse.

In analyzing whether the written description requirement is met, it is first determined whether the whether a representative number of species have been described by their complete structure. Since it is not realistic to expect that the "complete structure" of any transgenic animal, or even a cell, could be described, this requirement is interpreted to be whether phenotypic consequences or other characteristics of the animals resulting from altering the genotype have been described. In the instant case, the claimed invention invention encompasses any nonhuman mammal comprising a human cytochrome p450. Considering the fact that the claimed invention encompass transgenic animals as well as non transgenic animals, and there is no description of the phenotype of any mammal other than a mouse, the phenotype(s) of the claimed animals can not be predicted because the art of making transgenic animals or knockout animals is highly unpredictable. Even in the case of a transgenic mouse, the art teaches that phenotype of a transgenic mouse can not be predicted. Wood (Comparative Medicine 50 (1): 12-15, 2000) noted:

"The phenotype of an animal is determined by a complex interaction of genetics and environment. It is the evaluation of the phenotype that allows us to determine the usefulness of a mutant strain as a model for biomedical research.....A specific phenotype is usually expected from genetically altered mice whether they are transgenic over-expression models or gene knockout models where a particular gene function has been modified or ablated altogether. Thus for any given genetic alteration, we often try to predict what the phenotype will be. Many times we find the predicted phenotypes or more. It is, however, common to hear that surprisingly a given model has "no phenotype"."

Hammer et al (Hammer RE et al. Cell 63:1099-1112.1990) created both transgenic mice and rats expressing human HLA-b27 gene and beta-2 microglobulin. Although, both the transgenic animals bearing HLA-27 gene expressed the gene, transgenic mice did not show any HLA-2 associated disease whereas the transgenic rats demonstrated most of the HLA-B27 related diseases (see lines 20-28 in col 2 of page 1099). This shows that the integration of a transgene into alternative species may result in widely different phenotypic

responses even in animals of the same species. Additionally, promoters and enhancer elements may not function in all the species because they may require specific cellular factors.

This clearly indicates that the phenotype of a transgenic mouse or rat or any mammal can not be predicted. Therefore, the specification does not describe the phenotype of a representative number of species of the genus.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In the instant application, what would have been the result of expressing cytochrome p450 in any nonhuman mammal could not be predicted. With the limited information disclosed in the specification, an artisan would have not been able to predict whether the mammals would have had same or different phenotypes compared to the transgenic mouse. In the absence of sufficient description for the mammals, the cells derived from the mammals also lack sufficient description.

Therefore, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the huge genera recited in the claims at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genera.

8. Claims 1-5 and 7-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises a human CYP3A4 gene, wherein administration of substrate of the CYP3A4 gene encoded enzyme results in the expression of CYP3A4 enzyme, does not reasonably provide enablement for any non-human mammal comprising any human cytochrome 450. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to

make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claim 1 is drawn to a non-human mammal which harbors at least one human cytochrome p450 gene wherein the expression of the gene is induced by a compound serving as a substrate for a product of the gene. Claim 2 limits the p45o to CYPT3A family while claim 3 and 5 limit how the gene is introduced animal in which the gene encoding GPCR mACHR-6 is misexpressed or how the mammal is produced. Claim 9 recites a cell or tissue of the mammal.

The specification teaches working example of producing a mouse ES cell comprising a fragment of human chromosome 7 that contains the human CYP3A gene and preparation of a transgenic mouse by using the ES cells comprising the human chromosome 7 fragment and characterization of the mice (see examples 2-6). The art does not teach how to make any other mammal and does not teach what are the characteristics of any nonhuman mammal other than a mouse.

As the current state of the transgenic animal research stands, there are several significant limitations to the application of same methodology of making transgenic animals to different species. Longer gestation times, reduced litter sizes, number of fertilized eggs required for micro injection and relatively low

efficiency of gene integration and method of introduction of transgenes are a few examples of such limitations.

In a more recent assessment of the transgenic technology, Cameron (Cameron ER. Molecular Biotechnology 7:253-265, 1997) noted, " Well regulated transgene expression is the key to successful transgenic work, but all too often experiments are blighted by poor levels or the complete absence of expression, as well as less common problems, such as leaky expression in nontargeted tissues. A feature common to many transgenic experiments is the unpredictable transgenic lines produced with the same construct frequently displaying different levels of expression. Further, expression levels do not correlate with the number of transgene copies integrated. Such copy- number-independent expression patterns emphasize the influence of surrounding chromatin on the transgene" (see page 256, section 4 on transgene regulation and expression).

For example, Hammer et al (Hammer RE et al. Cell 63:1099-1112.1990) created both transgenic mice and rats expressing human HLA-b27 gene and beta-2 microglobulin. Although, both the transgenic animals bearing HLA-27 gene expressed the gene, transgenic mice did not show any HLA-2 associated disease whereas the transgenic rats demonstrated most of the HLA-B27 related diseases (see lines 20-28 in col 2 of page 1099). This shows that the integration of a transgene into alternative species may result in widely different phenotypic responses even in animals of the same species. Additionally, promoters and enhancer elements may not function in all the species because they may require specific cellular factors. The specification does not provide any guidance as to whether a given promoter used for expressing an exogenous gene in one animal would have been functional in other animals and even if the promoter may have been active, whether the level of the transgenic product produced would have been sufficient to produce a certain phenotype. If not, what steps would have been taken to address this issue?

Introduction of foreign DNA into fertilized oocyte , for example by micro injection, may result in random integration of the exogenous DNA into host chromosomal DNA which in turn may have major consequences on the expression of the transgene, therefore the production of transgene in all the non-human mammals species will be highly variable and unpredictable. Even if the transgenic animals are produced, it is highly unpredictable whether transgenic animals from species other than mouse (in the present case) will express the transgene to a level high enough so as to enable the development of the claimed phenotype in the transgenic animals.

The art of culturing and maintaining ES cells in culture is unpredictable. Gardner and Brook (Gardner RL and Brook FA. International J. of Dev. Biol. 41:235-243, 1997) summarized the progress in the field of ES cell biology, "Remarkably little is known about mammalian embryonic stem (ES) cells despite their very widespread use in studies on gene disruption and transgenesis. As yet, it is only in the mouse that lines of ES cells which retain the ability to form gametes following reintroduction into the early conceptus have been obtained. Even in this species, most stains have so far proved refractory to the derivation of cell lines....." Additionally, gene targeting and selection of the ES cells that harbor the integration of a desired construct also has been shown to be unprdictable in animals other than mice. To prevent their differentiation, ES cells are maintained in culture in the presence of mouse derived factors that inhibit differentiation either by coculturing the cells in the presence of feeder cell lines or by adding agents to the culture as a media supplement. However, it has been suggested that the such differentiation-inhibitory derived from mouse do not adequately prevent differentiation of stem cells in species other than the mouse

Even in 2002 the art of culturing ES cells was not routine as discussed by Prelle et al (Anat Histol Embryol 31:169-186, 2002; see the abstract). These authors noted:

"However, in spite of tremendous research activities, no proven ES cells colonizing the germ line have yet been established for vertebrate species other than the mouse (Evans and Kaufman, 1981; Martin, 1981) and chicken (Pain et al., 1996)."

Therefore, at the time of the invention, the art of culturing ES cells from any animal other than mouse was not routine. The specification as filed does not provide any guidance for maintaining and culturing the ES cell from any other murine species such as rat or hamster.

The art of transgenesis based on ES cells is unpredictable. The art of transgenesis based on ES cells is unpredictable. Seamark (Seamark, Reprod. Fertil. Dev. 6: 653-657, 1994) states that totipotency for ES cell technology in many livestock species has not been demonstrated (see abstract on page 653). He further adds that although various studies have provided insight into what this new technology could offer to the livestock breeder, scientific and technical challenge still confront the molecular and reproductive biologist attempting to make the technology available to serve this purpose (page 653, 3rd paragraph). Moreadith and Radford (J. Mol. Med. 75:208-216, 1997) state "...indeed, the creation of mutant animals, some of which have unpredictable and subtle phenotypes, has rekindled interest in developing techniques that allow one to characterize the animals precisely."

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictablility of the art, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to make any nonhuman mammal comprising any cytochrome p450 gene and therefore, limiting the scope of the claimed invention to a transgenic mouse whose genome comprises a human CYP3A4 gene, wherein administration of substrate of the CYP3A4 gene encoded enzyme to the transgenic mouse results in the expression of CYP3A4 enzyme. It is noted that the unpredictability of a particular area may alone provide reasonbale doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991).

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 is indefinite because it recites nonelected subject matter. Applicants are required to amend the claim to reflect the elected subject matter.

Claim 7 recites the limitation "wherein disruption of the cytochrome P450" gene is inherent to said nonhuman mammalian .....". There is insufficient antecedent basis for this limitation in the claim. Claim 4 does not recite any such limitation. Accordingly claim 4 is also indefinite.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-5 and 7-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Li et al (Archives of Biochemistry and Biophysics 329:235-240, 1996).

Li et al teaches transgenic mice expressing human cytochrome P450 CYP3A7 wherein the tissues of the mice express the enzyme and are activated in an Ames test (see the results in figures 1-5 and table 2). The art also teaches backcrossing of founder mice with the parental strain (see the materials and methods section).

Regarding claim 3, it is noted that the limitation that the p45o is introduced by introducing a YAC vector is immaterial since the claim is drawn to a mouse that expresses a human cytochrome P450 gene.

13. Claims 1-5 and 7-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Li et al (Biochem Biophys Res Comm 228:312-317, 1996).

Li et al teaches transgenic mice expressing human cytochrome P450 CYP3A7 wherein the tissues of the mice express the enzyme and are activated in an Ames test (see the results in figures 1-5). The art also teaches backcrossing of founder mice with the parental strain (see the materials and methods section).

Regarding claim 3, it is noted that the limitation that the p45o is introduced by introducing a YAC vector is immaterial since the claim is drawn to a mouse that expresses a human cytochrome P450 gene.

14. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (571) 272-0735 . The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. The fax phone number for TC 1600 is (703) 872-9306. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (571) 272-0532.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ram R. Shukla, Ph.D.
Primary Examiner
Art Unit 1632

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER